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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,099	09/12/2003	Andrew Vaillant	16051-5US	6577

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,099	VAILLANT ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *3-13,21-25 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 14-20, and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The pre-appeal conference panel has decided to withdraw the finality of the last Office action mailed on 25 August 2006. Claims 1-38 are pending. Claims 3-13, 21-25, and 33-38 are withdrawn. Claims 1, 2, 14-20, and 26-32 are under final rejection.

The nonstatutory double patenting rejection of claims 1, 2, 14-20, and 26-32 as being unpatentable over claims 1-3, 5, 7-10, 12-14, 18-20, 28, and 29 of copending Application No. 11/661,403 is maintained because the patent ownership clause is missing from the terminal disclaimer filed on 08 June 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1,2, 14-20 and 26-32 under 35 U.S.C. §112, 1st ¶, as containing subject matter which was not described in the specification commensurate in scope with the claims is maintained for reasons of record.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth

of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. MPEP §2164.01(a).

Nature of the invention. The claims are drawn to a method for the prophylaxis or treatment of a HIV infection in a subject, comprising administering to a subject a therapeutically effective amount of at least one pharmaceutically acceptable oligonucleotide (ODN) at least 30 nucleotides in length, wherein said ODN has an anti-HIV activity and wherein the anti-HIV activity of said ODN occurs principally by a sequence independent mode of action.

Breadth of the claims. The claims read on a genus of unspecified ODN that are at least 30-mers. The claims are of excessive breadth and encompass any give putative antiviral ODN without providing any meaningful structural limitations concerning that compound. The description in the specification simply fails to support such breadth in the claim language.

Working examples. The disclosure fails to provide any working embodiments that meet the claimed limitations. No *in vivo* working example of any ODN is disclosed in the specification. While there are cell culture examples for REP2006 (a random 40-mer) and REP2007 (a random 80-mer) that inhibit the replication of HIV *env* gene (Example 4 and Figure 19), the two compounds do not represent all ODN that fall within the scope of the invention and do not correlate with *in vivo* treatment and prophylaxis of HIV infection.

Guidance in the specification. The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to a cell culture assay to determine the IC_{50} (Figure 21-24). However, there is no evidence that shows any correlation with *in vivo* efficacy for three reasons. First of all, there is no structural guidance to the broad genus of unspecified ODN. In other words, the specification fails to disclose what part of an HIV is the target of inhibition and which chemical structures are critical for binding to HIV and

which structures are required for the sequence-independent anti-HIV activity. Thus, the specification is no more than an invitation by the applicants to further undue experimentation to identify putative sequence-independent anti-HIV ODNs and determine their structures. Secondly, there is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects. Lastly, there is not even a test to determine the efficacy and resistance of the claimed genus of ODN HIV inhibitors to confirm the cell culture inhibitory results. *In vitro* testing is, at most, a useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment and prophylaxis without any knowledge of the pharmacokinetic profile, therapeutic and/or prophylactic effect in a patient. Therefore, the disclosure does not correlate with treating HIV infection or preventing AIDS, especially when the subject may be a person.

State of the prior art. At the time the invention was made, an ODN of 30 or more nucleotides for the treatment or prophylaxis of HIV infection is not routine in the art. It has been well known in the prior art (Buss, 2001; Gait, 1995) that the development of suitable HIV-1 therapeutics has been an arduous and empirical process, often ending in failure. This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable *in vitro* and *in vivo* activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The challenges of developing

efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. For example, all of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development program at the earliest possible stage.

Predictability of the art. The art of HIV treatment is highly unpredictable because the effect of antiretroviral treatment appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to

develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

Amount of experimentation necessary. An ODN of at least 30 nucleotides for HIV treatment or prophylaxis is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an anti-HIV agent. Without sufficient guidance to the safety, tolerability, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances. For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Applicants argue that several scientific publications demonstrate that a macaque animal model infected with SIV and SIV-derived (chimeric) viruses shows the activity of antiviral drugs that are known to be active in humans and FDA approved (i.e. PMEA, PMPA, efavirenz, AZT, 3TC and lopinavir/ritonavir). However, the references provided by Applicants (Silvera, Van Rompay, Hofman, Yoshimura and North) disclose current HIV drugs that are not analogous to the claimed genus of 30-mer or larger ODN, which have different structure and mode of inhibition. The publications do not provide evidence to show that the drug studies in animal models are predictive of effectiveness in human subjects. Therefore, the disclosure in the cited references is not germane to the claimed invention.

The Juteau declaration under 37 CFR 1.132 filed on 8 June 2006 is insufficient to overcome the rejection of claims 1, 2, 14-20 and 26-32 based upon insufficiency of disclosure under 35 U.S.C. §112, first paragraph, because the facts presented are not germane to the rejection at issue and the scope of showing is not commensurate in scope with the claims. The

declaration presents an SIV model in one non-human primate, which is not scientifically conclusive, and an FLV model in mice, which is nonanalogous to the claimed method of prophylaxis and treatment of HIV in humans. FLV is a feline virus that is entirely different from the HIV in the claimed invention. SIV is a monkey virus that is presumed to be applicable to HIV albeit not a complete mimic to fully capture the complex interactions of natural HIV infection in humans (Hu, 2005). Most importantly, the SIV study is not meaningful for the following reasons: (1) the study experiments with only ONE macaque; (2) the study does not have any positive or negative control; (3) the study only lasts for 12 weeks; (4) the data shows only 3.5 folds reduction of viremia, from 1479300 virus copies per ml to 427217 copies per ml. The sample size is not statistically significant to demonstrate the effectiveness of REP2006 random 40-mer, especially with no comparison to a control group. The length of the study is not long enough to show HIV viral rebound or clearance. Given the large amount of virus remaining in the serum, the effectiveness of REP2006 is questionable and its therapeutic value is uncertain. Therefore, the data is invalid for the claimed invention of HIV treatment and prophylaxis.

Furthermore, it is well established in the art that non-human primate models are not predictive of HIV infection in humans until efficacy data becomes available from parallel studies in humans and macaques (Hu, 2005; Gallo, 2005). Accordingly, the data generated using *in vitro* assays, or from testing in an animal model, is not sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. MPEP §2164.02. [T]he issue of "correlation" is also dependent on the state of the prior art. Hu clearly teaches that the macaque model is not recognized as correlating to the HIV infection inside human bodies, one skilled in the art would not accept the model as reasonably correlating to the condition. *In re*

Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications).

The rejection of claims 1, 2, 14-20 and 26-32 under 35 U.S.C. §112, 1st ¶, as failing to comply with the written description requirement is maintained.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and~or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

For a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

In the instant case, the claims are drawn to a method comprising administering at least one pharmacologically acceptable oligonucleotide (ODN) at least 30 nucleotides in length, wherein said ODN has an anti-HIV activity and wherein the anti-HIV activity of said ODN occurs principally by a sequence independent mode of action. The newly amended limitation "sequence independent mode of action" encompasses all possible targets related to HIV, including any part of the HIV, e.g. Env, Gag, Tat, Nef, Vpr, Vpu, Vif, Rev, Pol, etc. Since there is no sequence requirement for the ODN, there is no common partial structure for all the species in the genus that correlates with the function of sequence-independent anti-HIV activity. Therefore, the claims are drawn to a genus of unspecified ODN that is defined only by a functional characteristic of anti-HIV activity. The claims encompass an inordinate number of species that are neither described nor contemplated by Applicants.

The specification only provides description for 16 ODN of at least 30 nucleotides (p. 104-106, Table 1). The 16 ODN in Table 1 are mostly randomers and disclose only the length of the ODN. Since the anti-HIV activity occurs in a sequence-independent manner, the disclosed sequences do not represent the structures of all species and do not adequately describe the

broad genus of ODN with such highly variant structures. Although the claims may recite some functional characteristics, the claims lack written description because there is no correlation between the structure and function of the claimed genus of ODN, especially the randomers. The specification does not support the ODN species there is no description of the structure of the randomers. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111 (page 1116).

As discussed above, the skilled artisan cannot envision the chemical structure and the correlated function of every unspecified species in the ODN genus as claimed. One skilled in the art can make a population of different randomly generated sequences of defined length, however, the skilled artisan would not know which of the randomers actually inhibit HIV in a sequence-independent manner as claimed. The instant application is analogous to the *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). Patent is directed to a method for inhibiting prostaglandin synthesis in human host using unspecified compound. Action by University of Rochester against G.D. Searle & Co. Inc., Monsanto Co., Pharmacia Corp., and Pfizer Inc. for patent infringement. District court granted defendants' motion for summary judgment of patent invalidity based on failure to satisfy written description and enablement requirements, and plaintiff appealed. Affirmed. The description in the specification does not support the inordinate number of species as claimed. As a result, one of skill in the art could not conclude that Applicant was in possession of the claimed ODN genus used in the method at the time of the invention. Therefore, claims 1, 2, 14-20 and 26-32 do not meet the written description provision of 35 U.S.C. §112, first paragraph.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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15 May 2007

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